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BY SIMON FLEXNER, M. D., *Associate in Pathology,*
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[From the Pathological Laboratory of the Johns Hopkins University and
Hospital.]

Presented by the author



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The bacillus diphtheriæ has by the more recent studies of the subject been shown to be present sometimes in pathological processes which do not present the characteristic features of diphtheria. Among these may be mentioned follicular or lacunar tonsillitis, fibrinous rhinitis and otitis media.* It has also been found, although associated as a rule with other micro-organisms, in infected wounds of the surface in persons who were not themselves suffering from diphtheria and who had not been exposed to the disease.† And in a comparatively few instances virulent forms of this organism have been found upon the mucous membrane of the healthy throat.‡

The significance of those cases in which the bacillus diphtheriæ is found in the body in the absence of the symptoms which usually accompany its presence, consists not so much in the danger threatening the host, as in the possibility of danger to other individuals, more susceptible perhaps, with whom such an infected person may come into contact. It is a growing belief that in just those cases in which the usual phenomena of diphtheria are wanting it is important to determine by bacteriological means the presence or absence of the Loeffler bacillus, for now, since attention has been directed to these atypical forms of diphtheria, reports of cases in which from

* Koplik, *New York Medical Journal*, 1892; Councilman, *American Journal of Medical Sciences*, November, 1893; Flexner, *American Journal of Medical Sciences*, March, 1895.

† Brunner, *Berliner klinische Wochenschrift*, 1893, Nos. 22, 23 and 24.

‡ Loeffler, Hoffmann, Fraenkel, Feer, and Park and Beebe.



a slight and unsuspected diphtheritic infection instances of typical diphtheria have taken their origin are not uncommon.*

These considerations have led us to report two cases in which recently the bacillus diphtheriæ has been isolated at autopsy from the membrane and exudate upon the gums and lips of two grown individuals. The appearances of the membrane in one and the exudate in the other case were in no way typical of diphtheria, and the cases obtain an additional interest from the fact that during life the patients presented no symptoms referable to the presence of the Loeffler bacillus. No other focus of diphtheria existed in the body as far as could be determined. The pharynx and larynx were both free from exudate or membrane, and thus while it must be assumed that in these cases the diphtheria bacilli often reached the mucous membrane of the pharynx, it must be admitted that arriving there they did no damage. The instances of laryngeal diphtheria in which the bacillus diphtheriæ can be found by cultures to be present upon the pharyngeal mucous membrane in the absence of any lesion in the latter situation are very well known.

The cases present, also, interesting examples of poly-infection with bacteria. That several different micro-organisms may coexist in the body, each producing its effect, perhaps each a peculiar effect, is a fact not very infrequently demonstrable at autopsies upon human beings, and yet it is one not much emphasized in writings upon infection. The frequency and variety of terminal infections with bacteria in the course of chronic diseases, as determined by the bacteriological study of the autopsy material of this laboratory, have recently been described elsewhere.† The cases here reported are offered as additional examples of multiple and terminal infections.

Both of the cases are from the medical wards (Prof. Osler) of the hospital.

Case 1.—J. P., white, aged 67 years. He had been in the hospital on three separate occasions, the first being on the 17th of January, 1894. His symptoms at that time pointed to arterio-

* E. Meyer, Berliner klin. Wochenschrift, 1894, p. 40. Felsen-thal, Münchener med. Wochenschrift, 1895, No. 3; Washbourn and Hopwood, British Medical Journal, Jan. 19, 1895.

† Welch: The Middleton Goldsmith Lecture, 1894.

sclerosis and chronic nephritis. The second admission was on June 29th, 1894, at which time he was suffering from a double tertian malarial infection. The last admission was on October 17 of the same year. At this time he was suffering from dyspnea and œdema of the legs. The urine was pale, its specific gravity never exceeded 1010, it was albuminous and always contained hyaline and granular casts. He incessantly scratched his legs, in consequence of which he developed a cellulitis of the left leg which was incised on January 17th, 1895. The subcutaneous tissue was found diffusely infiltrated, showing here and there pus pockets. Posteriorly there was a large abscess extending from the popliteal space, which it involved, to the heel. The suppuration was intermuscular, the fasciæ being dissected up and disintegrating. Muscles and periosteum were not involved. From the cover-slips and cultures streptococci were obtained. He died on January 20th.

Autopsy, January 21st (Dr. Flexner). The anatomical diagnosis was as follows: Chronic diffuse nephritis (small red granular kidneys); arterio-sclerosis; fibrous myocarditis; globular thrombi in right auricular appendage; heart hypertrophy; vegetative endocarditis (recent); sero-fibrinous pericarditis. Healed(?) tuberculosis of lungs; thrombosis of pulmonary artery without infarction; congestion and œdema of lungs. Tubercular peritonitis. Cirrhosis of liver. Cellulitis of leg. Acute gastritis. *Diphtheria of lips, gums and teeth.*

The following is the abbreviated protocol: Body 157 cm. long. Slightly built; emaciated. Oedema of ankles and hands. Suppuration of tissues of the left leg. *Oral cavity:* The mucous membrane of the lips is congested. Where the lips come in contact with the teeth there is to be seen upon the surface a greyish, necrotic-looking membrane, which upon removal leaves a defect in the epithelial covering of the mucous membrane. The resulting ulcer is deep red in color. The upper and lower lips are both affected, and the membrane is most marked over their central portions. The teeth are badly eroded, the crowns only retaining their enamel covering. The gums are somewhat retracted, and covering the exposed portion of the teeth, and in part the gums, there is a membrane similar to that upon the lips. The mucous membrane of the tongue

and pharynx is pale and free from membrane or exudate; the larynx also is free. *Peritoneal cavity*: It contains no excess of fluid. The peritoneum covering the lower zone of the abdomen, and particularly the pelvis, is covered with a large number of tubercles. These are either miliary or conglomerate in form; and some of them are surrounded by a zone of dark pigment. Tubercles also exist in the mesentery. *Intestines*: Except for some patches of congestion, nothing abnormal is to be seen. The mucous membrane is free from ulceration. *Stomach*: The mucous membrane is intensely congested and small ecchymoses and erosions are present within it. The surface is covered with sticky pus. *Pericardium and Heart*: The pericardial cavity contains 20 cc. of quite clear fluid, and both of its layers are covered with a fibrinous exudation, easily removed, and exposing congested vessels and small points of hemorrhage. The heart is hypertrophied and dilated. Upon the free border of the mitral valve several translucent, fresh vegetations are visible. The muscle of the apex is converted into fibrous tissue, and at this point there is a globular dilatation. The segments of the aortic valve are not shortened, but they are diffusely thickened. At the insertion of the middle segment a calcified patch occurs, upon which a fresh translucent thrombus is situated. The coronary arteries are extensively atheromatous. *Lungs*: The left shows retracted scars and small calcified areas. The right is free from tuberculous lesions. *Urinary bladder*: It is contracted and almost empty. The mucous membrane just above the trigonum is diffusely hemorrhagic, while in other parts it is injected and contains small ecchymoses.

Bacteriological Examination.—The bacteriological study embraced first the phlegmon of the left leg, the acute pericarditis, the vegetations on the heart valves and the acute cystitis. In the first and last streptococci were found in large numbers; in the other streptococci were also present, but in smaller numbers. The tubercles in the peritoneum were not examined for tubercle bacilli, but from their structure there can be no doubt that tubercle bacilli could have been demonstrated in them. The main interest, for the purposes of this paper, concerns the bacteriological study of the exudate upon the teeth, gums and lips, and the purulent material covering

the mucous membrane of the stomach. The cover-slips made at the autopsy showed many bacteria in the membrane and exudate upon the lips. Among these were diplococci, small and large bacilli and chains of bacilli. Upon the blood-serum tube inoculated from the exudate a good growth was obtained in 24 hours. Cover-slips from this showed as the predominating organism a thin bacillus three or four times as long as broad, and which showed a tendency to grow in small clumps the individuals being arranged side by side in nearly parallel lines, and also often placed at angles to one another. The size was, however, quite variable, some individuals being five or six times as long as broad. A more striking characteristic was the variation in form, for slightly curved forms were to be seen, as well as forms with swollen ends or swellings elsewhere in their substance. This irregularity was all the more distinct in that these swellings often possessed the property of staining more intensely than the remainder of the rods. This irregularity of staining was well brought out in preparations treated with Stirling's gentian violet stain, and subsequently with a 1:1000 solution of acetic acid. But Loeffler's methylene blue solution also sufficed to show the differences in a striking manner. Besides this bacillus only a coccus grew upon the blood serum, the greater number of organisms transplanted from the membrane refusing to be cultivated upon this medium.

From the morphology of the bacilli alone it seemed probable that the organism was the bacillus diphtheriæ, but to remove all doubt further tests were applied. The bacillus grown upon various media, namely, agar-agar, faintly alkaline bouillon, litmus bouillon and litmus milk, gave the following reactions. Upon agar-agar slants there was a faint growth along the line of the inoculation after 24 hours at 37° C. Later there was an increase in the width of the growth, but not in its thickness. It remained delicate and translucent. Single colonies upon agar-agar plates were not distinguishable from the colonies of a control culture. The ordinary bouillon and the litmus bouillon showed in 24 hours a faint cloudiness, which increased a little during the succeeding 24 hours and then remained stationary. A slight very finely granular sediment formed in the bottom of the tube, the

bouillon, however, not having been rendered clear thereby. The first effect upon the litmus was to redden it slightly, and, comparing it with a typical culture of the bacillus diphtheriæ obtained from a case of faucial diphtheria, it was found that the two cultures produced the same amount of reddening in twenty-four hours; nor was there any perceptible difference until the fourth day, when the culture from the throat, which was used as a control, showed a somewhat greater reddening than the other. The litmus milk pursued a similar course, except that in it the acid production went on more rapidly, the control culture again showing on the fourth day a more marked acid reaction.

A half-grown guinea-pig received subcutaneously on February 11, 1895, at 2 P. M., one cubic centimetre of a turbid suspension from an agar-agar culture several days old. A node corresponding with the seat of inoculation had formed by the next day, but the animal did not appear to be ill. On the 13th the node had increased in size, the animal was quiet, sat in one corner of the cage with its hair ruffled, and showed a disinclination to move. It ate little. By the 14th the node had further increased in size and had by this time become very hard. It was incised and the tissues were found to be infiltrated with a greyish-white firm fibrinous material. Cover-slips prepared from this material showed large numbers of the typical bacilli. After several days the animal seemed gradually to recover, it began again to eat, an ulcer formed at the seat of inoculation, and after two weeks it is still alive, although much emaciated. The ulcer has not yet healed.

From the properties which this organism exhibited there can be no doubt that it is the bacillus diphtheriæ, although not a form possessed of decided virulence.

The blood-serum culture from the stomach gave only two organisms. The predominating one was a short bacillus with sharpened ends, tending to grow in chains; and the other agreed with the bacillus isolated from the membrane upon the mouth both in form and in cultural properties. Its virulence was not tested upon animals.

To summarize this case, it is seen to have been one of chronic nephritis associated with arterio-sclerosis, heart hyper-

trophy and cirrhosis of the liver, in which there was a triple infection: 1, old tubercular lesions in the lungs and tubercular peritonitis; 2, streptococcus cellulitis, pericarditis and endocarditis; 3, diphtheria of the gums, lips and stomach. It may be questioned whether the diphtheria bacillus is to be considered the cause of the acute gastritis, and it must be admitted that the data at hand do not permit of a conclusion upon this point. But that the bacillus diphtheriæ may cause actual diphtheritic processes in the stomach has been shown by the bacteriological study of some cases associated with faucial diphtheria; and the variety of inflammations in the throat with which this bacillus is associated makes it more probable still that it may give rise under exceptional circumstances to an acute gastritis such as was present in this case.

Case 2.—A. R., white, aged 36 years, was admitted to the medical wards, January 30, 1895. He complained of dropsy and dyspnoea. On admission there was general oedema, which continued until death. *Lungs:* The patient had several attacks of brisk hæmoptysis. The cough was severe; the expectoration blood-tinged. On the evening of February 1st he had a chill, and the temperature, which hitherto had been subnormal, now rose to 102° F., and ranged from 100°–103° until the 9th inst., when it fell to normal. During these 8 days the signs were: dulness and flat tympany over the right upper lobe, with tubular respiration and large crackling, resonant râles. Breathing tubular. When the temperature fell on the 9th it was regarded as the crisis. The upper lobe did not clear up, tubular respiration with fine crackling râles being still heard on the 12th. On the 11th the temperature again rose, and it pursued a fluctuating course, ranging from 105.6° to 99° for two days. On the 13th dulness was found over the upper left front, and the vocal resonance was increased. A pure leucocytosis, reaching at its height 40,000, was present during the last days of life. *The urine* contained albumin, red blood corpuscles, pus and epithelial cells and blood, waxy, hyaline, granular and epithelial casts in abundance. Death occurred on the 14th inst.

Autopsy, February 15th (Dr. Flexner). *Anatomical Diagnosis:* Lung tuberculosis with cavity formation; chronic interstitial pneumonia with tubercular bronchiectatic cavities.

Acute lobar pneumonia. Chronic diffuse nephritis (large white kidneys). Tuberculosis of the bronchial, tracheal and mesenteric glands. Fatty degeneration of the heart. *Diphtheria of lips.*

An abstract of the protocol is as follows: Body 170 cm. long, strongly built and well nourished. There is œdema of the extremities and face. *Lips:* They are covered with a greyish-white exudate, which, upon the separation of the upper and lower lips, adheres principally to the lower one. This exudate can be easily removed with the finger, and there is no defect of the epithelium visible beneath it. *Lungs:* The upper lobe of the right lung is occupied by several cavities, the largest one being situated at the apex. The substance of the lung between the cavities is firm, pigmented and indurated. In the anterior portion there is a diffuse tuberculous infiltration, undergoing softening. Numerous small bronchiectatic cavities with caseous walls are present in this portion of the lung. Miliary and conglomerate tubercles exist in the indurated tissue of this lobe. In the apex of the left lung are two depressed pigmented scars. The entire upper lobe is consolidated, granular, and grey in color. There is no evidence of resolution in this lobe. The lower lobe is congested and œdematous. *Kidneys:* Together they weigh 475 grams. The average dimensions are 12.5x7x4 cm. The cortex measures 9 mm. The two kidneys are alike. The capsule strips off easily; the surface in general is pale, but shows a slight mottling with red. On section the striæ are coarse, the surface is œdematous, the glomeruli are pale. The consistence of the organs is diminished. *Pharynx:* The mucous membrane is pale and free from exudation. *Larynx:* A few superficial losses of substance occur in the mucous membrane, being most numerous over the true vocal cords. *Frozen sections* of the kidneys show the epithelium of the labyrinthine tubules to be granular and fatty. The tubules in the pyramidal portion contain at times blood-coloring matter. An occasional cast is met with in the tubules. The interstitial tissue is increased in foci.

Bacteriological Examination.—From the lung cavity tubercle bacilli and many encapsulated diplococci were found in cover-slips. From the consolidated lobe of the left lung the micrococcus lanceolatus was obtained. But of especial interest is

the result of the study of the exudation upon the lips. Cover-slip preparations made from the exudate showed a variety of bacteria, among which the bacillus diphtheriæ was not recognized. The blood-serum culture gave, however, after 24 hours at 37° C., a growth in which the predominating organisms were a bacillus which morphologically resembled the bacillus diphtheriæ and a streptococcus. Discrete colonies containing one or both of these organisms were present upon the first tube, the majority of the transplanted bacteria having refused in this as in the previous case to grow upon the blood serum.

The bacilli were tested upon blood-serum, agar-agar, alkaline bouillon, litmus bouillon, litmus milk and potato, and compared with a known control culture. The bacilli from the exudate behaved in a characteristic manner in general, showing, however, one or two variations. In bouillon a slight sediment formed in the first 24 hours, which increased in the next 24 hours and then remained stationary, but a slight cloudiness persisted in the fluid. The bacilli were non-motile. On potato, after 24 hours at 37° C. there was no visible growth, but cover-slip preparations showed that there had been an increase of the organisms. At the end of the next 24 hours a slight greyish-white growth could be seen upon the potato. The litmus bouillon was rendered red in 48 hours in about an equal degree with the control culture. The litmus milk reaction was typical. Blood-serum to which an infusion of litmus had been added before coagulating the serum so as to obtain a blue medium, served excellently for demonstrating the acid-producing power of the organisms. There is a more rapid multiplication and more abundant growth of the bacilli upon it and, in consequence, a greater acid formation. The first appearance of red is in the water of condensation which collects at the lower part of the tube between it and the culture medium; the red color gradually extends over the surface and also into the depth. The final effect is to produce a diffuse and intense reddening of the previously blue culture medium, which shows especially well when viewed with reflected light.

A half-grown guinea-pig was inoculated subcutaneously with a solid culture, and at the site of inoculation there developed a well-marked local reaction in 2 days. The

animal looked ill. At the time of writing (10 days after the inoculation) the animal still lives.

To summarize this case, it was one of chronic pulmonary phthisis and Bright's disease, the terminal event of which was an acute lobar pneumonia, to which was added in the last days of life an infection with the bacillus diphtheriæ.

There can be but little doubt, we think, that in both of these cases the diphtheria developed during the last days of life, although in the first instance the reaction was much greater than in the last. As the first patient had been in the hospital for a number of weeks, it is probable that the infection originated in the hospital. In the same ward a nurse developed a typical case of diphtheria just about the time of his death, and may easily enough have been the source of infection, although a reverse order is not to be excluded. These cases remind one, moreover, of the small group of cases of latent diphtheria which Heubner* has just reported as occurring in children, in which the disease developed insidiously and was unsuspected until laryngeal stenosis suddenly developed, or the fact was revealed at autopsy. The affected children had been in hospitals suffering from some chronic disease.

* Berliner klin. Wochenschrift, December, 1894.

